PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appellant: Dipak K. Banerjee, *et al.*	Group Art Unit: 1623
Application. Number: 09/779,447	Examiner: Howard V. Owens, Jr.
Filed: February 9, 2001	
For: METHODS FOR INHIBITING ANGIOGENESIS	**APPEAL BRIEF**

This is an appeal from the final Office Action dated May 17, 2004 (Paper 15), of the examiner's final rejection of claims 9, 14 and 18.

I. Real Party in Interest.

The University of Puerto Rico is the assignee and owner of the patent application and the real party in interest.

II. Related Appeals and Interferences.

There are no related other appeals or interferences known to appellants which will directly affect or be directly affected by or have a bearing on the Boards decision in this appeal.

III. Status of the Claims.

Claims 2-18 were pending in the application. These claims stand rejected by the examiner under 35 U.S.C. §103 as being unpatentable over Banerjee, *et al., Is asparagine-linked protein glycosylation an obligatory requirement for angiogenesis?,* Indian J. Biochem. and Biophysics, Vol. 30(6), pp.389-94 (1993) (hereinafter "Banerjee 1993") and Tiganis, *et*

al., Functional and Morphological Changes Induced by Tunicamycin in Dividing and Confluent Endothelial Cells, Exp. Cell Research, Vol. 198, pp. 191-200 (1992) (hereinafter "Tiganis 1992").

IV. Status of Amendments.

After filing the notice of appeal, applicants requested entry of amendments to claims 9 and 14 so that these claims would stand in independent form. Applicants further requested cancellation of claims 2-8, 10-13, 15-17 and 19-92, without prejudice. At the time this appeal brief is being filed, the examiner had not yet entered this amendment.

V. Summary of the Invention.

The invention relates to the inhibition of angiogenesis in a patient, which is useful in the treatment of diabetic retinopathy, atherosclerotic plaques, scleroderma, hypertrophic scarring, vascular adhesions, angiofibroma, trachoma graft neovascularization, corneal graft neovascularization, neovascular glaucoma, thrombosis, restenosis, osteoporosis, macular degeneration, arthritis, hemangiomas, psoriasis and tumors. More specifically, the invention relates to the safe administration of tunicamycin to patients for this purpose.

A. Background of the Invention.

Over seven years prior to filing the patent application which is the subject of this appeal, Prof. Dipak K. Banerjee (one of the inventors) published the article titled *Is asparagines-linked protein glycosylation an obligatory requirement for angiogenesis?* (again "Banerjee 1993"). This article investigated the basic, biologic link between glycosylation and angiogenesis. Through *in vitro* studies, Banerjee 1993 concluded that these two processes are linked. In reaching this conclusion, Banerjee 1993 relied upon the results from

a number of disclosed experiments including one showing that tunicamycin inhibited glycosylation.

Banerjee 1993, however, was limited to *in vitro* studies. The subject article neither taught nor suggested that tunicamycin (nor any of the other compounds used in the disclosed experiments) could be administered *in vivo,* let alone in human patients, to treat angiogenesis. This is confirmed by the declaration of Prof. Dipak K. Banerjee, which is attached hereto as Exhibit A and incorporated herein by reference.

Although, as the examiner appears to concede, Banerjee 1993 does not extend its teachings to *in vivo* applications, the examiner further relies upon a contemporaneous article titled *Functional and Morphological Changes Induced by Tunicamycin in Dividing and Confluent Endothelial Cells* (again "Tiganis 1992"). This article investigated the effect of tunicamycin on endothelial cells. As with Banerjee 1993, Tiganis 1992 disclosed experiments that were conducted *in vitro.* Regarding the possible extension of the disclosed experiments to *in vivo* applications, Tiganis 1992 expressly warned that such an application would cause "damage to brain microvessels in tunicamycin-treated animals." (Page 199.) Tiganis 1992, therefore, is fairly viewed for the teaching that tunicamycin could <u>not</u> be administered to human patients to inhibit angiogenesis for the obvious reason that brain damage would be an unacceptable side effect.

B. <u>Claimed Aspects of the Invention.</u>

Against the above teaching, which would prevent administering tunicamycin to a human patient for fear of causing brain damage, the subject patent application demonstrates that tunicamycin can be administered for the treatment of angiogenesis-related diseases. The precise dosage regime is explained in detail in the specification. And, this invention is

expressly set forth in the claims at issue on appeal. For example, claim 18 recites in pertinent part:

> administering tunicamycin in an amount effective to inhibit angiogenesis, to a patient in need of such treatment;
> wherein the tunicamycin is administered for a period of about 1 week to 6 months at a daily dosage of about 5 to 20 mg/kg of body weight.

In addition, the subject patent application further demonstrates that treatment of angiogenesis by the administration of tunicamycin should be suspended for a period of time. As the specification explains, this permits the patient to recover from any adverse reactions and likewise improves patient response. (See page 46.) This further aspect of the invention is expressly set forth in the claims at issue on appeal. For example, claim 18 recites in pertinent part:

> wherein the tunicamycin is administered for a period of about 1 week to 6 months at a daily dosage of about 5 to 20 mg/kg of body weight, subsequently the administration of the tunicamycin is suspended for a period of about 1 week to 6 months, and subsequently the tunicamycin is administered for a period of about 1 week to 6 months at a daily dosage of about 5 to 20 mg/kg of body weight.

VI. Issues

Whether the examiner's combination of Banerjee 1993 and Tiganis 1992 fairly teaches or suggests applicant's claimed invention?

Applicants' Answer: NO

Neither Banerjee 1993 nor Tiganis 1992 fairly teaches or suggests the administration of tunicamycin *in vivo*. And, when fairly viewed as a whole, these references would appear to teach away from the claimed invention because Tiganis 1992 teaches that the administration of tunicamycin would cause brain damage. The subject patent application teaches a method of safely and effectively administering tunicamycin to human patients. This method is expressly recited in the claims at issue on appeal and nowhere taught or suggested by the prior art relied upon by the examiner.

VII. Grouping of Claims

For the convenience of the Board in reviewing the examiner's rejections, the claims are grouped so that those with similar claim elements or combinations of claim elements may be evaluated together. Notwithstanding such grouping, the precise wording of the claims differ in ways that may be material either to the application of any additional prior art against the claims or to an infringement analysis of the claims. Appellant respectfully submits that these groupings are made solely for purpose of this proceeding. Appellant respectfully reserves the right to distinguish the precise wording of the claims in any further or subsequent proceedings.

In view of the forgoing, claim 9 stands alone and claims 14 and 18 stand together. Each of these three claims recite the administration of tunicamycin to a patient to inhibit angiogenesis, and further recite that such treatment is suspended for a period of time. Neither of the references relied upon by the examiner fairly teach or suggest these elements. Indeed, when the prior art relied upon by the examiner is fairly viewed as a whole, it teaches away from administration of tunicamycin to a human patient because of the adverse side effect of brain damage. For these and the reasons, the examiner's rejections should be reversed.

In addition, claims 14 and 18 further recite the specific dosage which the applicants have determined is safe for administration to a patient. These claims are grouped together with respect to this further element.

VIII. Argument

A. Legal Standard

The examiner bears the burden of establishing a *prima facie* case of obviousness. In re Deuel, 34 U.S.P.Q.2d 1210, 1214 (Fed. Cir. 1995). Only if this burden is met does the

burden of coming forward with rebuttal argument or evidence shift to the appellant. Id. To establish a *prima facie* case of obviousness the examiner must provide references which alone or in combination teach each and every element of the claimed invention. In re Fine, 837 F.2d 1071, 1074, 5 U.S.P.Q. 2d 1596, 1598 (Fed. Cir. 1988). When relying upon a combination of references, the teaching or suggestion to modify the references or to make the claimed combination must be found in the prior art, not in appellant's disclosure. In re Vaeck, 947 F.2d 488, 20 U.S.P.Q.2d 1438 (Fed. Cir. 1991).

When the references cited by the examiner fail to establish a *prima facie* case of unpatentability, the rejection is improper and will be overturned. In re Deuel, 34 U.S.P.Q. 2d at 1214. Under these circumstances, the appellant is entitled to a grant of a patent. In re Oetiker, 24 U.S.P.Q.2d 1443, 1444 (Fed. Cir. 1992).

For the reasons set forth below, the examiner's rejections of claims 9, 14 and 18 fail to establish a *prima facie* case of obviousness. When fairly viewed as a whole, the prior art references upon which the examiner relies teach away from applicants' claimed invention.

B. Non-Obviousness

Each of the claims at issue recites: (1) administering tunicamycin in an amount effective to inhibit angiogenesis to a patient in need of such treatment; and (2) suspending, then re-administering the treatment. (In addition, claims 14 and 18 recite the specific dosage at which tunicamycin is safely administered in humans.)

Banerjee 1993 investigates the link between glycosylation and angiogenesis. In connection with that investigation, Banerjee 1993 discloses various *in vitro* experiments, one of which involves tunicamycin. Banerjee 1993, however, nowhere teaches or even remotely suggests that tunicamycin could be administered to a human patient. The examiner does not contend otherwise.

Tiganis 1992 expressly teaches that the administration of tunicamycin *in vivo* would cause damage to brain tissue. Given this expected side effect, Tiganis in no way suggests that tunicamycin be administered to a human patient. In fairness, the expectation of brain damage teaches away from the administration of tunicamycin *in vivo.*

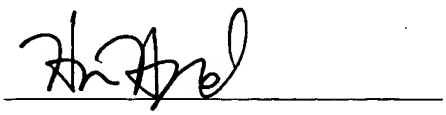
Against this background, the subject patent application teaches that tunicamycin can, in fact, be safely administered to a patient. (And, claims 14 and 18 recite the specific dosage.) The claims at issue recite this treatment, which includes the suspension then re-administration of tunicamycin. Since neither of the prior art references relied upon by the examiner contemplated *in vivo* administration of tunicamycin to a patient, neither reference even contemplates the further improvement of suspending then re-admistering the treatment. For these reasons, the examiner has failed to establish a *prima facie* case of obviousness. In fact, when fairly viewed as a whole, Banerjee 1993 and Tiganis 1992 teach away from applicants' claimed invention.

IX. Conclusion.

For the reason set forth above, appellant respectfully submits that the cited references fail to teach or fairly suggest applicants' claimed invention. In fact the cited references teach away from applicants' claimed invention. Accordingly, the subject claims stand in condition for allowance and the examiner's rejection should be reversed.

Respectfully submitted,

October 21, 2004

By: 

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Appendix A

Claim 9: A method for inhibiting angiogenesis, comprising:

administering a nucleoside in an amount effective to inhibit angiogenesis, to a patient in need of such treatment, the nucleoside comprising glucosamine, and wherein the glucosamine comprises at least one tunicamycin and functional derivatives thereof, and wherein the at least one of tunicamycin and factional derivatives thereof is administered for a period of time, subsequently the administration of the at least one of tuniumycin and functional derivatives thereof is suspended for a period of time of at least about 1 week, and subsequently the administration of the at least one of tunicamycin and functional derivatives thereof is resumed.

Claim 14: A method for inhibiting angiogenesis, comprising:

administering a nucleoside in an amount effective to inhibit angiogenesis, to a patient in need of such treatment, the nucleoside comprising glucosamine, wherein the glucosamine comprises at least one of tunicamycin and functional derivatives thereof, and wherein the glucosamine is administered for a period of about 1 week to 6 months at a daily dosage of about 5 to 20 mg/kg of body weight, subsequently the administration of the glucosamine is suspended for a period of about 1 week to 6 months, and subsequently the glucosamine is administered for a period of about 1 week to 6 months at a daily dose of about 5 to 20 mg/kg of body weight.

Claim 18: A method for inhibiting angingenesis, comprising:

administering tunicamycin in an amount effective to inhibit angiogenesis, to a patient in need of such treatment;

wherein the tunicamycin is administered for a period of about 1 week to 6 months at a daily dosage of about 5 to 20 mg/kg of body weight, subsequently the administration of the tunicamycin is suspended for a period of about 1 week to 6 months, and subsequently the tunicamycin is administered for a period of about 1 week to 6 months at a daily dosage of about 5 to 20 mg/kg of body weight.

EXHIBIT A

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Application. Number: 09/779,447	Examiner: Howard V. Owens, Jr.
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For: METHODS FOR INHIBITING ANGIOGENESIS	**DECLARATION OF DIPAK K. BANERJEE, PH. D.**

I, Prof. Dipak K. Banerjee, hereby declare as follows:

BACKGROUND

1. I hold a B.S. in Chemistry, from the University of Calcutta, India, a M.S. in Biochemistry from the University of Calcutta, India, and a Ph. D. in Biochemistry, from the University of Calcutta, India.

2. I have held the following professional positions:

Research Associate, Department of Biological Chemistry University of Maryland, School of Medicine, Baltimore, Maryland (03/79 - 06/80); Research Associate, Laboratory of Experimental Pathology, NIADDK, NIH, Bethesda, Maryland under Intergovernmental Personnel Agency Act from the University of Maryland School of Medicine, Baltimore, Maryland (07/80 - 09/82); Visiting Associate, LCBG, National Institute of Arthritis, Diabetes, Digestive and Kidney Diseases, NIH, Bethesda, Maryland (10/82 - 09/83); Biochemist, CIPCB, National Institute of Dental Research, NIH, Bethesda, Maryland (10/83 - 06/86); Associate

Professor, Department of Biochemistry, School of Medicine, University of Puerto Rico, San Juan, Puerto Rico (06/86 - 06/94); Professor, Department of Biochemistry, School of Medicine, University Puerto Rico, San Juan, Puerto Rico (07/94 – Present); Visiting Professor, Center for Cancer Research, Massachusetts Institute of Technology, Cambridge, MA (05/95-07/95); Visiting Professor, Center for Hygiene and Medical Microbiology, Philipps University, Marburg, Germany (05/97-06/97); Visiting Professor, Physical Biosciences Division, Earnest Orlando Lawrence Berkeley National Laboratory, Berkeley, CA (07/10/2000-08/11/2000); Visiting Professor, Physical Biosciences Division, Earnest Orlando Lawrence Berkeley National Laboratory, Berkeley, CA (04/01/2001-06/15/2001)

3. In view of my education and experience, I believe that I would qualify as a person skilled in the art to which the above-identified patent application relates.

PRIOR ART

3. In 1993 I published *Is asparagine-linked protein glycosylation an obligatory requirement for angiogenesis?*, Indian J. Biochem. and Biophysics, Vol. 30(6), pp.389-94 (1993) (hereinafter "Banerjee 1993"). As the title suggests, Banerjee 1993 investigated the basic, biologic link between glycosylation and angiogenesis. Through *in vitro* studies, Banerjee 1993 concluded that these two processes are linked. In reaching this conclusion, Banerjee 1993 relied upon the results from a number of disclosed experiments including one showing that tunicamycin inhibited glycosylation.

4. Banerjee 1993, however, was limited to *in vitro* studies. The subject article neither taught nor suggested that tunicamycin (nor any of the other compounds used in the disclosed experiments) could be administered *in vivo*, let alone in human patients, to treat angiogenesis. And, at the time Banerjee 1993 was published, I did not contemplate the possibility of admisitering tunicamycin to a human patient.

5. An article published approximately one year earlier, namely Tiganis, *et al.*, *Functional and Morphological Changes Induced by Tunicamycin in Dividing and Confluent Endothelial Cells,* Exp. Cell Research, Vol. 198, pp. 191-200 (1992) (hereinafter "Tiganis 1992") warned that the administration of tunicamycin *in vivo* would cause "damage to brain microvessels in tunicamycin-treated animals" (Page 199). Tiganis 1992, therefore, is fairly viewed for the teaching that tunicamycin could not be administered to human patients to inhibit angiogenesis for the obvious reason that brain damage would be an unacceptable side effect.

6. When viewing the teachings of Banerjee 1993 together with Tiganis 1992 and stepping back in time, it is my opinion that these articles do not teach or fairly suggest my invention as set forth in claims 9, 14 and 18. In fact, I believe that these articles when taken together teach away from administering tunicamycin to human patients.

7. The methods expressly recited in claims 9, 14 and 18 are directed to dosage regimes that permit the safe administration of tunicamycin to a patient in need of treatment. For these reasons, I believe that they set forth patentable subject matter.

8. All statements made herein of my own knowledge are true and all statements made on information and belief are believed to be true; and further these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. §1001.

Respectfully submitted,

October 20, 2004

Dipak K. Banerjee, Ph. D.